

Manipulating your mind

What will science discover about our brains, and how are we going to deal with it?

The Decade of the Brain, proclaimed by US President George Bush in 1990, passed without making much of an obvious impact. But it did in fact produce considerable scientific advances in neurobiology, giving scientists an exponentially increasing knowledge of how the brain works and the means to manipulate biochemical processes within and between nerve cells. This knowledge is slowly trickling down to society as well, be it in the pharmaceutical industry, to parents concerned about their child's performance in school, to students looking for chemical helpers to pass their exams, or to military researchers who have an obvious interest in keeping soldiers awake and alert.

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The ability to fiddle with the brain with ever-increasing effectiveness has also created critical questions about how to use this knowledge. Francis Fukuyama, in *Our Posthuman Future*, Leon Kass, Chairman of the US President's Council on Bioethics, and Steven Rose, a neurobiologist at the Open University, UK, are the most prominent and outspoken critics of the use of psychopharmaceuticals and other neurological techniques to analyse and interfere with human mental capabilities. Their concerns have also grasped the attention of neurobiologists, ethicists, philosophers and the lay public, who are all slowly realising the enormous potential of modern neuroscience. "People closely identify themselves with their brains, they don't with their genes," said Arthur L.

Caplan, Professor of Bioethics at the University of Pennsylvania, Philadelphia, PA, USA.

Although these debates started in the late 1990s, it took the general public a bit longer to take notice—*The New York Times* and *The Economist* did not pick up on the issue until 2002. "There is a great amount of information about the brain but no one's paying attention to the ethics," Caplan said. "The attention of ethicists went to genetics because of the Human Genome Project...so we had to jump-start the ethics [in neurobiology]." But that is rapidly changing. Unlike the many claimed applications of genetics, such as gene therapy or molecular medicine, diagnostic and therapeutic products from neurobiological research are already available. Caplan sees four major controversial areas: the definition and diagnosis of certain types of behaviour, such as aggression, terrorism or poor performance in school; the use of drugs to alter such behaviour; questions about moral responsibility—with people going to court and saying 'this man isn't responsible because his brain is abnormal'; and eventually new debates about racial and gender differences.

These controversies are not just anticipated: most are already occurring. Society's pursuit of perfection entails 'treating' whatever is not desirable—be it bad mood, aggression or forgetfulness. Many people take herbal memory enhancers, such as *ginkgo biloba*, even though they are probably no more effective than sugar or coffee. But neurobiology adds a new twist. By understanding the brain's workings at the chemical level, it paves the way for much more efficient ways to tweak brain function. And many psychopharmaceuticals already enjoy a much broader popularity beyond

treating neurological and psychiatric diseases. "When you think of the millions of pills that people take as anti-anxiety drugs, how many of these people are really anxious? Probably just a small percentage," said James L. McGaugh, Director of the Center for the Neurobiology of Learning and Memory at the University of California, Irvine, CA, USA. Millions of school children in the USA are prescribed antipsychotic drugs or are treated for depression and attention deficit and hyperactivity disorder (ADHD), and the numbers in Western Europe are also increasing (Brower, 2003). There is an epidemic of new behavioural disorders: ADHD, seasonal affective disorder (SAD), post-traumatic stress



disorder (PTSD), panic disorder (PD), narcissistic personality disorder (NPD), borderline personality disorder (BPD), antisocial personality disorder (APD), histrionic personality disorder (HPD)—soon we will run out of letter combinations to abbreviate them all.

The explosive increase in prescriptions for Ritalin® for school children has already prompted questions about the apparent epidemic of ADHD. "Now it's not that Ritalin is not effective in sedating an over-active kid, it certainly is, but it's turning a complex social relationship into a problem inside the brain of a child and therefore inside the genes of a child," said Rose (see interview, in this issue).

In a way, Ritalin is neuroethics "in a nutshell", commented Wrye Sententia, co-director of the Center for Cognitive Liberty and Ethics (CCLE), a non-profit education, law and policy center in Davis, CA, USA, and head of its programme on neuroethics. The debate over the drug covers social, ethical and legal issues: who defines behaviour and behavioural disorder, who should control treatment, how should society react to drug misuse, and is it ethical to use drugs to gain an advantage over others? These are valid questions that apply equally to neuroethics in general.



Neuropharmaceuticals have already found applications outside a medical setting. Like amphetamines before it, Ritalin is increasingly used by healthy people to help them focus their attention. Similarly, the development of new drugs to influence the biochemistry of brain function also has broad economic potential outside the medical setting. Most memory-enhancing drugs available to treat Alzheimer's, such as donepezil, galantamine or rivastigmine, inhibit cholinesterase to slow down the turnover of the neurotransmitter acetylcholine

in the synapse. New drugs in the development pipeline will act on other compounds in the biochemical pathway that encodes memory: Cortex Pharmaceuticals (Irvine, CA, USA) are studying compounds called Ampakines®, which act on the AMPA receptor. This receptor responds to glutamate, which is itself involved in memory acquisition. Another class of drugs under development acts on the cAMP responsive element-binding protein (CREB), the last step in establishing long-term memory. "What we would expect is that drugs that enhance CREB signalling would be specific to inducing long-term memory and not affect upstream events of memory, such as memory acquisition and short term memory," explained Tim Tully, Professor at Cold Spring Harbor Laboratory (NY, USA) and founder of Helicon Therapeutics (Farmingdale, NY, USA), one of two companies now working on drugs to increase CREB function.

None of these drugs, however, tackles brain degeneration itself, the cause of Alzheimer's and other neurodegenerative diseases, but instead they delay the disease by squeezing a little more out of the remaining brain material. Consequently, they will also work on healthy people. Not surprisingly, the pharmaceutical industry has a great interest in this non-medical use of memory-enhancing drugs, according to McGaugh: "The Alzheimer market is a very important one, but small. The real market is everyone else out there who would like to learn a little easier. So they take a pill in place of studying harder."

Tully warned about the dangers of this off-label use of memory enhancers. The side effects of the first generation of memory drugs are a risk that should not be taken when there is no reason, he said. And this may never become an application, due to other intrinsic side effects. "Maybe it is not a good thing to have memory enhanced chronically every day for the rest of your life. Maybe that will produce psychological side effects, like cramp your head with too many things you can't forget," Tully said.

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Although memory is important, so too is the ability to forget negative experiences. As long-term memory is largely enhanced by stress hormones and emotional arousal, a horrendous event can overload the system and lead to PTSD: patients persistently re-experience the trauma. Researchers at Harvard University are now studying propranolol, a beta-blocker commonly used as a cardiac drug, as a means to decrease PTSD. Similarly, Helicon Therapeutics is working on CREB suppressors to achieve the same goal: forgetting unwanted memories. These drugs could be valuable for rape victims, survivors of terrorist attacks or young soldiers suffering from PTSD as a result of battlefield experiences. Nevertheless, an ethical debate over memory suppressors has emerged. Kass has described them as the "morning-after pill for just about anything that produces regret, remorse, pain or guilt" (Baard, 2003). But "if the soldier should be shot in the leg, he is treated. They mend the wounds. Now why wouldn't they mend the mental wounds? On what moral grounds?" countered McGaugh. "We need the right regulations and we need the right education of society so that the social acceptance of how to use such drugs is appropriate," said Tully. "Just to give the drug to every soldier that has been out in the field, that would be an abuse... A commander-in-chief, one would hope, would decide against such a use based on his education and on his advisors telling him scientists and experts have discussed this issue and it's immoral to do something like that."

"Freedom of thought is situated at the core of what it means to be a free person"

Cognitive enhancement is of just as much military interest as the treatment of PTSD. German fighter pilots in World War II took amphetamines to stay alert during British bombing raids at night. During the war against Iraq, US fighter and bomber pilots used drugs to keep awake during the long flights to and from their targets, which with briefing and debriefing could easily exceed 24 hours. Not surprisingly, the US Air Force is carrying out research on how donepezil could improve pilots' performance. The strong military interest in psychopharmaceuticals also presents another conundrum: if the military allows their off-label use, it would be hard to call for a ban on their civil use, as Kass has suggested.

Neurological advances are not limited to new drugs. Brain imaging techniques, such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), offer enormous potential for analysing higher behaviour. While neurologists originally used them to analyse basic sensual, motor and cognitive processes, they are now increasingly being used by psychologists and philosophers to investigate the mechanics of social and moral attitudes, reasoning and moral perceptions (Illes *et al*, 2003). Joshua Greene, a graduate student at Princeton University's Center for the Study of Brain, Mind and Behavior, put his human subjects into a fMRI scanner and presented them with hypothetical scenarios in which they had to make a decision between two more or less bad outcomes of the situation (Greene *et al*, 2001). The results of the studies show how the brain weighs emotional and rational reasoning against each other in its decision-making. Potentially, this could be used as a sophisticated lie detector to see if someone answers a question spontaneously or after considerable reasoning. Other studies showed that the brain reacts differently at first sight when seeing a person of the same or a different skin colour (Hart *et al*, 2000; Phelps *et al*, 2000). That does not necessarily mean that everyone is a racist, but refinement of such methods could unveil personal prejudices or preferences. The use of brain scans to evaluate people's talents or dispositions will therefore draw as much interest as the drugs used to manipulate them. "Parents will be falling over themselves to take these tests," Caplan said. In contrast to Kass and other conservative critics, he therefore argues that regulation will not make sense but that it should be left to the individual to make decisions about whether to undergo diagnostic tests for behaviour or take behaviour-modifying drugs. "Medicine, business and the public will have to negotiate these boundaries," Caplan said, but he remains worried that "peer pressure and advertising and marketing will make us take those pills." Rose also does not call for a ban, but wants society to take control of these new advances and their applications, based on democratic decisions.

The use of these new tests and drugs may cause another problem. Going back to Ritalin, Sententia explained that an important reason for the apparent increase in ADHD may be overcrowded classrooms and overworked teachers, who are quick to label a child with ADHD rather than call for

improvements in the school. "From the top down there is a clear message to put these kids on drugs," Sententia said. Society should instead "put the parents' rights back into focus" and better educate parents about behavioural disorders. This would give them more freedom to make their own decisions for their child "so they are not at the mercy of doctors or teachers," she continued. Such "cognitive liberty", as Sententia described it, would have to rest on better public education and understanding about the risks and benefits, the potentials and myths of neurobiology. "What I think we need to do in the next five or ten years is discuss exactly what is appropriate and inappropriate in applying these things," said Tully. "Now is the time for education."

This does not, however, solve the question of who controls diagnostic tools and treatment in the case of people who are not free or able to make their own decisions—such as children, prison inmates or psychiatric patients. CCLE, for instance, filed an *amicus curiae* ('friend of the court') brief to the US Supreme Court on behalf of Charles T. Sell, to argue against a court order requiring Sell to be injected with psychotropic drugs to make him mentally competent to stand trial for insurance fraud. Sententia sees some limitations, however, to cognitive freedom. Children do not enjoy the same civil rights as adults, but it should be the parents—not teachers or schools—who make the decisions about the diagnosis and treatment of their children, she said. Prison inmates also lose some of their individual rights when they are convicted, Sententia continued, and this may include their right to refuse medication. "The legal system will have to decide how to use this knowledge about the brain," Caplan commented, in light of the "tremendous tension between brain privacy and social interest in controlling dangerous behaviour." Sententia therefore stressed that all decisions about diagnosis and treatment must at least be in accordance with the US Constitution and the United Nations Declaration of Human Rights.

Some of the most important applications of this right to privacy concern using brain scans as a sophisticated lie detector for prisoners seeking parole, foreigners applying for a visa or employers testing their employees' honesty. "What and how you think should be private," Sententia said, because "freedom of thought is situated at the core of what it means to be a free person." Caplan also

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expects more pressure from society in future to make sure that no such tests are performed without informed consent.

Equally, Caplan, Sententia and others believe that individuals should be free to use neurological technology to enhance their mental abilities outside a medical setting. This is in contrast to the prohibitive stance taken by Kass and other conservatives who argue that it would be neither 'natural' nor fair to those who choose not to use such enhancement. "It's not clear to me that all forms of enhancement are bad," commented Adina Roskies, a neuroscientist and philosopher at the Massachusetts Institute of Technology's Department of Linguistics and Philosophy (Cambridge, MA, USA). "There are all sorts of things that we do today that enhance our life prospects and that are not considered to be bad. ... We're far away from the 'natural' order already." Thus, in some cases, instead of controlling or even restricting these new possibilities, it would be better if society focuses on trying to ensure that everyone has access to them, she continued. Given the increasing interest that the public is showing in the new possibilities offered by neuroscience, it may be too late for restrictions anyway. "There is no way of stopping this tide, the genie is out of the bottle," Sententia said, "so the question is: how can we navigate this sea of change?"

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